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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,744	04/24/2001	Jorge F. DiMartino	12636-891	5759

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WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 943041050

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,13,14,16-28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 13, 14, 16 and 18-26* is/are rejected.

7)☒ Claim(s) *17,27,28 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/1/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *2004-09-16* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 4, 13, 14, 16-28 and 30 are pending.

Applicants' amendment filed on June 23, 2004 is acknowledged, and applicants' response has been fully considered. Claims 1, 4 and 28 have been amended, and claims 5-12, 29 and 31-38 have been cancelled. Thus, claims 1, 4, 13, 14, 16-28 and 30 are examined.

Objection Withdrawn

2. The previous objection of claim 28 is withdrawn in view of applicant's amendment to the claim in the amendment filed June 23, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1, 4, 9-14, 16-28 and 30 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at pages 5-6 of the amendment filed June 23, 2004.

4. The previous rejection of claim 4 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 6 in the amendment filed June 23, 2004.

Claim Objections

5. Claim 1 is objected to because of the use of the term "MS-27-275", which a chemical name should be provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 19 recites the limitation "the cyclic peptide" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 20-22 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

8. Claim 23 recites the limitation "the butyrate" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 24-26 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 4, 13, 14, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santini *et al.* (Annals of Internal Medicine, 134, 573-586 (April 3, 2001)) in view of Cameron *et al.* (Nature Genetics 21, 103-107 (January 1999)).

Santini *et al.* teach aberrant CpG island hypermethylation in cancer is associated with transcriptional silencing of gene expression and indicate it plays an important role as an alternate mechanism by which tumor suppressor genes are inactivated in cancer (page 574, right column). Various cancers including solid tumors, malignant hematologic diseases, myelodysplastic syndromes, and chronic myelogenous leukemia are treated with different doses of a DNA methylation inhibitor, decitabine or 5-azacytidine (pages 578-582), one example indicates elderly patients with high risk myelodysplastic syndrome were treated with decitabine at dosage 40-50 mg/m^2 over 24 hours with continuous infusion for 3 days every six weeks and later with 15 mg/m^2 over 4 hours every 8 hours for 3 days every six weeks (page 581, right column; Table 5; claims 1, 4, 13 and 14, 16 and 18). Although Santini *et al.* do not disclose using a specific histone deacetylase inhibitor in the treatment of cancer, the reference does suggest the use of decitabine or 5-azacytidine with other drugs such as histone deactylase (HDA) inhibitors in the combination therapy (page 583; claim 1). Cameron *et al.* disclose several tumor suppressor genes such as MLH1, TIMP3, CDKN2B and CDKN2A, which are hypermethylated genes and silenced in the cancer cells, are re-expressed in the presence of low dose 5-aza-2'deoxycytidine (100 or 500 nM, or 1 μM) and trichostatin A (300 or 500 nM; page 103, right column; page 104, left column; page 106, left column). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to be motivated to combine the two references to treat cancer using decitabine or 5-azacytidine taught by Santini *et al.* in combination with a specific HDA inhibitor, trichostatin A as indicated by Cameron *et al.* because the use of decitabine and trichostatin A would reactivate the expression of hypermethylated genes and potentiate the differentiation response of the agents as indicated by Santini *et al.* (page 583). Thus, the

combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

10. Claims 1, 4, 13, 14, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santini *et al.* (Annals of Internal Medicine, 134, 573-586 (April 3, 2001)) in view of Zhu *et al.* (Cancer Research 61, 1327-1333 (February 15, 2001)).

Santini *et al.* teach aberrant CpG island hypermethylation in cancer is associated with transcriptional silencing of gene expression and indicate it plays an important role as an alternate mechanism by which tumor suppressor genes are inactivated in cancer (page 574, right column). Various cancers including solid tumors, malignant hematologic diseases, myelodysplastic syndromes, and chronic myelogenous leukemia are treated with different doses of a DNA methylation inhibitor, decitabine or 5-azacytidine (pages 578-582), one example indicates elderly patients with high risk myelodysplastic syndrome were treated with decitabine at dosage 40-50 mg/m^2 over 24 hours with continuous infusion for 3 days every six weeks and later with 15 mg/m^2 over 4 hours every 8 hours for 3 days every six weeks (page 581, right column; Table 5; claims 1 4, 13 and 14, 16 and 18). Although Santini *et al.* do not disclose using a specific histone deacetylase inhibitor in the treatment of cancer, the reference suggests the use of decitabine or 5-azacytidine with other drugs such as histone deacetylase (HDA) inhibitors in the combination therapy (page 583; claim 1). Zhu *et al.* teach HDA inhibitors, depsipeptide (FR901228, e.g., 0.5 μM) and trichostatin A (e.g., 0.5 μM) induce apoptotic cell death of human lung cancer cells, and this induced apoptosis is greatly enhanced in the presence of the DNA methylation inhibitor, 5-aza-2'-deoxycytidine (1 μM; Fig. 1; pages 1328). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to be

motivated to combine the two references to treat cancer using decitabine or 5-azacytidine taught by Santini *et al.* in combination with a specific HDA inhibitor, trichostatin A or depsipeptide as indicated by Zhu *et al.* because 5-aza-2'-deoxycytidine can enhance the apoptosis of cancer cells induced by HDA inhibitor and the use of HDA inhibitor could potentiate the response of the agents as indicated by Santini *et al.* (page 583). Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Claim Objections

11. Claims 17, 27, 28 and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. Claims 1, 4, 13, 14, 16 and 18-26 are rejected, and claims 17, 27, 28 and 30 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

JON WEBER
SUPERVISORY PATENT EXAMINER

CMK
September 16, 2004